Ruthenium-catalyzed C–H/O–H and C–H/N–H bond functionalizations: oxidative annulations of cyclopropyl-substituted alkynes†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 142Monica Deponti,^a Sergei I. Kozhushkov,^a Dmitry S. Yufit^b and Lutz Ackermann*^aReceived 1st July 2012,
Accepted 11th October 2012

DOI: 10.1039/c2ob26250a

www.rsc.org/obc

The chemical behavior of cyclopropyl-substituted alkynes has been probed using the reaction conditions of ruthenium-catalyzed oxidative C–H/O–H and C–H/N–H bond functionalizations. The oxidative annulations proceeded with complete conservation of all cyclopropane fragments and allowed for the one-step preparation of synthetically useful cyclopropyl-substituted isocoumarins and isoquinolones with high regioselectivities and chemical yields. The connectivities of the key heterocyclic products were unambiguously established by X-ray diffraction analysis.

Introduction

Transition metal-catalyzed reactions have matured to being among the most powerful tools in organic chemistry.¹ Particularly, direct functionalizations² of aromatic C–H bonds have received considerable recent attention as ecologically and economically friendly synthetic methods, that avoid the use of prefunctionalized starting materials. Yet, an even more sustainable strategy is represented by the simultaneous transition metal-catalyzed C–H/O–H or C–H/N–H bond functionalizations utilizing arenes or alkenes **1** (Scheme 1).

This approach allowed for the one-pot preparation of synthetically useful heterocycles **3**, such as substituted isoquinolinones, isoquinolones, isocoumarins, α -pyrones and 2-

pyridones, many of which possess valuable biological activities^{3a–e} and represent key structural scaffolds of naturally occurring compounds.^{3f–i} Consequently, a number of valuable protocols for intermolecular oxidative annulations with alkynes **2** have been developed,^{4,5} with ruthenium-catalyzed⁴ cyclizations being among the most promising.

The attachment of a cyclopropyl fragment to heterocyclic molecules frequently modifies their pharmacological properties and significantly enhances their biological activities.⁶ For instance, a number of well-known antibacterial agents, such as Ciprofloxacin, Sparfloxacin, Grepafloxacin and WIN-57294, contain a 1-cyclopropylquinolin-4(1*H*)-one moiety.^{6e,f} However, the inherently high molecular strain in cyclopropanes (28.1 kcal mol^{−1})⁷ is reflected by some specificity to the chemistry of cyclopropane-containing molecules. As a consequence, metal-mediated or -catalyzed reactions with participation of (cyclopropylcarbonyl) metal intermediates proceeded almost exclusively *via* opening of at least one cyclopropane ring,⁸ whereas formation of cyclopropane-containing compounds was observed as a side reaction only. Given the remarkable biological activity of cyclopropyl-decorated heterocycles along with the challenges associated with the use of cyclopropyl-substituted alkynes **2** in transition-metal catalysis, we, thus, became attracted to exploring their unprecedented oxidative annulations by metal-catalyzed C–H/Het–H bond functionalization with rather inexpensive ruthenium catalysts, on which we wish to report herein.

Scheme 1 Oxidative annulations by C–H/O–H or C–H/N–H bond functionalizations.

^aInstitut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen, Germany.

E-mail: lutz.ackermann@chemie.uni-goettingen.de; Fax: +49 (551) 396777

^bDepartment of Chemistry, University of Durham, Durham, South Rd., DH1 3LE, UK.

E-mail: d.s.yufit@durham.ac.uk

†Electronic supplementary information (ESI) available: Experimental details of syntheses and X-ray diffraction, ¹H NMR spectra and ¹³C NMR spectra of new compounds. CCDC 901337 (**6aa**), 901338 (**6ae**), 901339 (**7aa**), 901340 (**8aa**) and 901341 (**8ah**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26250a

Results and discussion

To elucidate the synthetic versatility of the transformation as well as the influence and reactivity of cyclopropyl substituents

Fig. 1 Substituted ethynylcyclopropanes **2**, benzoic acids **4** and benzamides **5** used in C–H/Het–H bond functionalizations.

in the alkynes **2**, we set out to perform detailed synthetic and structural studies on atom- and step-economical ruthenium-catalyzed C–H/O–H and C–H/N–H bond functionalizations of representative benzoic acids **4a–d** and benzamides **5a–i** with various cyclopropylacetylenes **2** (Fig. 1).

We initiated our studies by exploring the reactivity of substituted benzoic acids **4** and cyclopropylarylethyne **2** in ruthenium-catalyzed oxidative annulations^{4f} (Scheme 2). Notably, arylalkynes displaying a cyclopropyl substituent yielded the desired product through the C–H/O–H bond functionalizations

Scheme 2 Ruthenium-catalyzed C–H/O–H bond functionalizations with benzoic acids **4** and (cyclopropylethynyl)benzenes **2**. ^a[RuCl₂(*p*-cymene)]₂ (5 mol %).

reaction manifold. Thus, the highest yield was observed for the alkyne **2a** in the reaction with the acid **4c**, while the yield decreased with alkyne **2e** possessing an electron-withdrawing substituent. However, the influence of the substituents in benzoic acids **4** was found to be less pronounced.

No product formation was observed in the reactions of substrate **4a** with alkyne **2d** and when using starting materials **4d** and **2a**, while the corresponding isocoumarin **6dk** was formed in the reaction of **4d** with diethylethyne in 31% yield.[†]

The influence of the cyclopropyl moieties upon the course of chemical transformations by the stabilization of key reaction intermediates due to conjugation is well documented.⁹ However, several representative experiments with *p*-anisic acid (**4b**) and selected alkynes **2** (Table 1) indicated the cyclopropyl substituents in the alkynes **2** to translate into a reduction of their reactivity (entry 1), but demonstrated no significant influence onto the regioselectivity of the annulation. Indeed, the reaction with (pent-1-ynyl)cyclopropane (**2h**) furnished a 1 : 1 mixture of the two regioisomeric isocoumarins **6bh** and **7bh** (entry 2), thereby indicating a negligible effect of steric interactions¹⁰ in these annulations. Furthermore, the electronic effect of the cyclopropane appeared to be of less importance for the overall regioselectivity.

It is noteworthy that the rhodium-catalyzed annulation of unsymmetrically substituted arylalkyl alkynes Alk–C≡C–Ar delivered mixtures of 3- and 4-arylsubstituted regioisomeric products^{11,12} in ratios of 6 : 1 to 8 : 1.^{5i,j} In spite of the previously reported almost exclusive formation of 3-arylsubstituted products,^{4e} the cyclization of alkyne **2i** afforded in our hands heterocycles **7bi** and **6bi** in a ratio of 9.4 : 1 (Table 1, entry 3).

In the ruthenium-catalyzed cyclizations of unsymmetrical cyclopropylacetylenes the ratios of regioisomeric products **6** and **7** varied from 1 : 1 to 13 : 1 (Scheme 2 and Table 1). To

Table 1 Ruthenium-catalyzed C–H/O–H bond functionalizations with *p*-anisic acid (**4b**) and selected substituted alkynes **2**

Entry	Alkyne	R ¹	R ²	Product 6/yield (%)	Product 7/yield (%)
1	2g	<i>c</i> Pr	<i>c</i> Pr	6bg = 7bg	7bg /27
2	2h	<i>c</i> Pr	<i>n</i> Pr	6bh / 7bh	1 : 1/53
3	2i	Et	Ph	6bi /47	7bi /5

Fig. 2 Molecular structures of isocoumarins **6aa**, **6ae** and **7aa** in the crystal¹³ (numbering does not correspond to the IUPAC rules).

elaborate spectroscopic criteria[†] for this group of cyclopropyl-substituted heterocycles, the structures of cyclopropylisocoumarins **6aa**, **6ae** and **7aa** have been unambiguously established by X-ray diffraction analysis (Fig. 2). Notably, both 3-aryl-4-cyclopropyl-substituted heterocycles **6aa** and **6ae** adopted essentially the same conformations with the dihedral angles C1–C2–C3–center (C4–C5) being equal to -99.5° and -96.8° , respectively, while the dihedral angles between heterocyclic and carbocyclic aromatic moieties were found to be 47.3° and 37.6° , respectively. In contrast, in **7aa** the dihedral angle C1–C2–C3–centre (C4–C5) = 179.4° with the angle between aromatic planes of 66.5° , *i.e.* with almost ideal conditions for the conjugation of cyclopropyl and isocoumarin fragments.[†]

Somewhat similar tendencies were observed in ruthenium-catalyzed C–H/N–H bond functionalizations in benzamides **5** with (cyclopropylethynyl)benzenes **2**, the results of which are summarized in Scheme 3. Generally, the oxidative annulations occurred with high yields and synthetically useful regioselectivity. While the catalytic system displayed a high functional group tolerance, the attempted cyclization of amide **5a** with cyclopropyl-naphthylalkyne **2d** gave less satisfactory results.[†] Furthermore, cyclopropylaryl alkynes **2c** and **2e** possessing electron-withdrawing substituents on the aromatic rings delivered the corresponding products **8ac** and **8ae**, respectively, in somewhat lower yield. However, a number of oxidative cyclizations, including the reaction of the parent compounds **2a** and **5a**, proceeded in a regioselective manner affording only regioisomers **8** (**8aa**, **8ac**, **8ae**, **8af** and **8ca**), while in the other cases the ratio of heterocycles **8** and **9** varied from 9.8 (**8ia**) to 3.6 (**8ab**). Surprisingly, the best yield (83%) was obtained when utilizing dicyclopropylacetylene (**2g**), which was less reactive in the ruthenium-catalyzed isocoumarin synthesis (*vide supra*). Unfortunately, the attempted synthesis of *N*-cyclopropyl-3(4)-cyclopropylisoquinolones **8ea** and **9ea** occurred less efficiently. Moreover, the benzamide **5e** did not react with diphenylacetylene (tolane) under otherwise identical reaction conditions.

Remarkably, the nitrogen substituent had a considerable effect on the outcome of the annulation. Thus, *N*-Me- (**5a**),

Scheme 3 Ruthenium-catalyzed C–H/N–H bond functionalizations in benzamides **5** with (cyclopropylethynyl)benzenes **2**.

N-Et- (**5b**), *N*-*n*Bu- (**5d**) and *N*-iso-propylbenzamides (**5c**) furnished the corresponding isoquinolones **8** and **9** in the reactions with the alkyne **2a** in 71, 39, 39 and 23% yield, respectively. This is in line with the values of steric substituent constants of these alkyl groups, which are equal to 0, 0.86, 0.86 and 2.29, respectively.¹⁰ Yet, in contrast to the synthesis of isocoumarins, the reaction of cyclopropyl-*n*-propyl alkyne (**2h**) with benzamide **5a** afforded a 2.75 : 1 mixture of 3-cyclopropyl (**9ah**) and 4-cyclopropylisoquinolones (**8ah**) (Scheme 3), in spite of the steric substituent constants being equal to 0.89 (*n*-propyl) and 1.33 (cyclopropyl).¹⁰

The exact connectivities of the parent isoquinolone **8aa** and of the fundamentally important compound **8ah** have been established by X-ray diffraction analysis (Fig. 3). As for the

Fig. 3 Molecular structures of isoquinolones **8aa** and **8ah** in the crystal¹³ (numbering does not correspond to the IUPAC rules).

Scheme 4 Regiochemistry-determining step of the ruthenium-catalyzed C-H/Het-H and C-H/N-H bond functionalizations.

analogous isocoumarins **6aa** and **6ae**, heterocycles **9aa** and **9ah** adopted essentially the same conformations with the dihedral angles C1–C2–C3–center (C4–C5) equal to 94.7° and 91.7°, respectively, *i.e.* without steric preconditions for conjugation, while the dihedral angle between heterocyclic and phenyl aromatic moieties in **8aa** was determined to be 63.2°.

It is particularly noteworthy that all the ruthenium-catalyzed oxidative C-H/Het-H bond functionalizations proceeded with complete conservation of all cyclopropane fragments.^{8,14} As a consequence, cyclopropylethyne can be utilized in ruthenium-catalyzed C-H/Het-H bond functionalizations for the preparation of valuable cyclopropyl-substituted heterocycles. According to the mechanistic rationalizations generally accepted for ruthenium-catalyzed C-H/Het-H bond functionalization with alkynes,^{4a,b,d–g} the regiochemistry-determining step of these oxidative reactions is constituted by the insertion of alkyne **2** into the ruthenium–carbon bond of key intermediate **10** to give the seven-membered ruthenacycle **11** (Scheme 4). Thus, the observed regioselectivities can for instance be rationalized by the enhanced thermodynamic stability of regioisomer **11**, in which the aryl substituent is in the neighboring position to the ruthenium.

Conclusions

In summary, we have examined the behavior of cyclopropyl-substituted acetylenes in the ruthenium-catalyzed oxidative C-H/O-H and C-H/N-H bond functionalizations and have found these reactions to proceed with complete conservation of all cyclopropane fragments. Thereby, these cyclizations allowed the one-step preparation of synthetically useful cyclopropyl-substituted isocoumarins and isoquinolones in high yields and regioselectivities.¹⁵

Experimental

Syntheses: general methods

Catalytic reactions were carried out using pre-dried glassware. Triethylamine and *t*AmOH were distilled over CaH₂ and sodium, respectively. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl. (Cyclopropylethynyl) benzene (**2a**), 1-(cyclopropylethynyl)-3-methylbenzene (**2b**), methyl 4-(cyclopropylethynyl)benzoate (**2c**), 1-(cyclopropylethynyl)naphthalene (**2d**), 1-(cyclopropylethynyl)-4-methoxybenzene (**2f**), the previously unknown 1-(cyclopropylethynyl)-3-(trifluoromethyl)benzene (**2e**), (pent-1-ynyl)cyclopropane (**2h**), 1,2-dicyclopropylethyne (**2g**), *N*-cyclopropylbenzamide (**5e**), *N*,3-dimethylbenzamide (**5f**), 4-chloro-*N*-methylbenzamide (**5g**), 4-methoxy-*N*-methylbenzamide (**5h**), 4-fluoro-*N*-methylbenzamide (**5i**) and [RuCl₂(*p*-cymene)]₂ were synthesized as indicated in the ESI.† Other chemicals were obtained from commercial sources and were used without further purification. Yields refer to isolated compounds, estimated to be >95% pure as determined by ¹H-NMR and GC. TLC: Macherey-Nagel, TLC plates Alugram® Sil G/UV₂₅₄. Detection under UV light at 254 nm. Chromatography: Separations were carried out on Merck Silica 60 (0.040–0.063 mm, 70–230 mesh ASTM). All IR spectra were recorded on a BRUKER ALPHA-P spectrometer. MS: EI-MS: Finnigan MAT 95, 70 eV; ESI-MS: Finnigan LCQ. High resolution mass spectrometry (HRMS): APEX IV 7T FTICR, Bruker Daltonic. M.p.: Stuart® Melting Point Apparatus SMP3 melting point apparatus, values are uncorrected. ¹H, ¹³C, ¹⁹F NMR-spectra were recorded at 300 (¹H), 75.5 (¹³C, APT (Attached Proton Test)) and 283 MHz (¹⁹F), respectively, on a Varian Unity-300 instrument.

Synthesis of cyclopropyl-substituted isocoumarins **6** and **7**

GENERAL PROCEDURE FOR RUTHENIUM-CATALYZED C-H/O-H BOND FUNCTIONALIZATIONS IN BENZOIC ACIDS **4 WITH ETHYNYLBENZENES **2**.** A suspension of acid **4** (2.00 mmol), alkyne **2** (1.00 mmol), [RuCl₂(*p*-cymene)]₂ (15.5 mg, 2.5 mol%), KPF₆ (36.8 mg, 20 mol%) and Cu(OAc)₂·H₂O (300 mg, 1.50 mmol) in *t*AmOH (3.0 mL) was stirred at 120 °C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with sat. aq. NH₄Cl–NH₃ solution (1 : 1, 50 mL) and extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with NH₄Cl–NH₃ solution (1 : 1, 2 × 20 mL) and dried over MgSO₄. After filtration and concentration of the solution under reduced

pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane–EtOAc 25 : 1) to yield **6** and **7** as colorless solids.

4-CYCLOPROPYL-3-PHENYL-1*H*-ISOCHROMEN-1-ONE (**6aa**) AND 3-CYCLOPROPYL-4-PHENYL-1*H*-ISOCHROMEN-1-ONE (**7aa**). According to the general procedure, benzoic acid (**4a**) (490 mg, 4.0 mmol), alkyne (**2a**) (284 mg, 2.0 mmol), [RuCl₂(*p*-cymene)]₂ (62.0 mg, 100 μmol), KPF₆ (73 mg, 0.4 mmol) and Cu(OAc)₂·H₂O (599 mg, 3.0 mmol) yielded compounds **6aa** (353 mg, 67%) and **7aa** (64 mg, 11%) as colorless solids. **6aa**: m.p. = 115–117 °C; ¹H NMR (300 MHz, CDCl₃) δ = 8.33 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.12 (d, *J* = 8.2, 1H), 7.78 (td, *J* = 7.7, 1.41 Hz, 1H), 7.76–7.72 (m, 2H), 7.50 (td, *J* = 7.7, 1.1 Hz, 1H), 7.46–7.37 (m, 3H), 1.91 (tt, *J* = 8.1, 5.5 Hz, 1H), 1.00–0.87 (m, 2H), 0.26–0.06 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ = 162.4 (C), 153.4 (C), 139.7 (C), 134.4 (CH), 133.2 (C), 129.5 (CH), 129.4 (CH), 129.3 (CH), 127.8 (CH), 127.7 (CH), 124.5 (CH), 120.6 (C), 114.5 (C), 9.9 (CH₂), 9.0 (CH); IR (ATR): 3011, 2961, 2922, 2855, 1718, 1629, 1078, 700 cm^{−1}; MS (EI) *m/z* (%): 262 (M⁺, 100), 247 (50), 234 (35), 165 (65), 69 (25); HRMS (EI) *m/z* calcd for C₁₈H₁₄O₂ (M⁺) 262.0994, found 262.0988.

7aa: m.p. = 100–102 °C; ¹H NMR (300 MHz, CDCl₃) δ = 8.20 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.57–7.33 (m, 7H), 6.95 (ddd, *J* = 8.1, 1.1, 0.5 Hz, 1H), 1.70–1.56 (m, 1H), 1.21–1.12 (m, 2H), 0.81–0.70 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ = 162.0 (C), 154.2 (C), 138.8 (C), 134.4 (CH), 134.2 (C), 131.0 (2CH), 129.3 (CH), 128.8 (CH), 127.9 (CH), 126.7 (CH), 123.9 (CH), 119.5 (C), 115.0 (C), 12.0 (CH), 7.6 (CH₂); IR (ATR): 3084, 3049, 3008, 2984, 1727, 1604, 1075, 672 cm^{−1}; MS (EI) *m/z* (relative intensity): 262 (M⁺, 50), 217 (45), 185 (40), 105 (55), 77 (100); HRMS (EI) calcd for C₁₈H₁₄O₂ (M⁺) 262.0994, found 262.0996.

The connectivities of compounds **6aa** and **7aa** were established by X-ray crystal structure analysis.¹³

4-CYCLOPROPYL-6-METHOXY-3-PHENYL-1*H*-ISOCHROMEN-1-ONE (**6ba**) AND 3-CYCLOPROPYL-6-METHOXY-4-PHENYL-1*H*-ISOCHROMEN-1-ONE (**7ba**). According to the general procedure, *p*-anisic acid (**4b**) (152 mg, 4.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), [RuCl₂(*p*-cymene)]₂ (31 mg, 50 μmol), KPF₆ (73 mg, 0.4 mmol) and Cu(OAc)₂·H₂O (599 mg, 3.0 mmol) yielded **6ba** (308 mg, 53%) and **7ba** (23 mg, 4%) after column chromatography as colorless solids. **6ba**: m.p. = 144–146 °C; ¹H NMR (300 MHz, CDCl₃) δ = 8.27 (d, *J* = 8.8 Hz, 1H), 7.75–7.71 (m, 1H), 7.50 (d, *J* = 2.5 Hz, 1H), 7.46–7.40 (m, 2H), 7.06 (dd, *J* = 8.8, 2.5 Hz, 1H), 3.97 (s, 2H), 1.88 (tt, *J* = 8.1, 5.5 Hz, 1H), 0.98–0.88 (m, 1H), 0.23–0.15 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ = 164.6 (C), 162.3 (C), 154.2 (C), 142.2 (C), 133.4 (C), 131.9 (CH), 129.6 (CH), 129.6 (CH), 129.5 (CH), 127.9 (CH), 115.5 (CH), 114.4 (C), 113.9 (C), 107.7 (CH), 55.7 (CH₃), 10.0 (CH₂), 9.2 (CH); IR (ATR): 3005, 2956, 2856, 1711, 1600, 1444, 1226, 831 cm^{−1}; MS (EI) *m/z* (%): 292 (M⁺, 95), 217 (36), 215 (77), 105 (90), 77 (100); HRMS (EI) calcd for C₁₉H₁₆O₃ (M⁺) 292.1099; found 292.1099.

7ba: m.p. = 126–128 °C; ¹H NMR (300 MHz, CDCl₃) δ = 8.22 (d, *J* = 8.8 Hz, 1H), 7.54–7.34 (m, 5H), 6.94 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 3.72 (s, 3H), 1.67–1.55 (m, 1H), 1.23–1.13 (m, 2H), 0.85–0.74 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ = 164.6 (C), 161.9 (C), 155.0 (C), 141.4 (C), 134.5 (C),

131.9 (CH), 131.1 (CH), 129.0 (CH), 128.0 (C), 115.1 (C), 114.6 (CH), 113.0 (C), 107.1 (CH), 55.6 (CH₃), 12.2 (CH), 7.8 (CH₂); IR (ATR): 3009, 2925, 1713, 1600, 1231, 1044, 849, 723 cm^{−1}; MS (EI) *m/z* (%): 292 (M⁺, 100), 277 (32), 264 (55), 195 (35), 152 (50); HRMS (EI) calcd for C₁₉H₁₆O₃ (M⁺) 292.1099, found 292.1105.

Synthesis of cyclopropyl-substituted isoquinolones **8** and **9**

GENERAL PROCEDURE FOR RUTHENIUM-CATALYZED C–H/N–H BONDS FUNCTIONALIZATIONS IN BENZAMIDES **5** WITH (CYCLOPROPYLETHYNYL)BENZENES **2**. A mixture of benzamide **5** (0.50 mmol), acetylene **2** (1.00 mmol), [RuCl₂(*p*-cymene)]₂ (15.3 mg, 25 μmol, 5.0 mol%) and Cu(OAc)₂·H₂O (200 mg, 1.00 mmol) in *t*AmOH (2.0 mL) was stirred at 100 °C under a nitrogen atmosphere for 22 h. After cooling the mixture to ambient temperature, the reaction mixture was diluted with aq. NH₃ solution (75 mL, 1.0 wt%) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over Mg₂SO₄. After filtration and concentration of the solution under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane–EtOAc 4 : 1) to yield **8** and **9** as colorless solids.

4-CYCLOPROPYL-2-METHYL-3-PHENYLISOQUINOLIN-1(2*H*)-ONE (**8aa**). According to the general procedure, *N*-methylbenzamide (**5a**) (135 mg, 1.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), [RuCl₂(*p*-cymene)]₂ (31 mg, 50 μmol), and Cu(OAc)₂·H₂O (399 mg, 2.0 mmol) yielded **8aa** (185 mg, 71%) after column chromatography as a colorless solid, m.p. = 139–141 °C; ¹H NMR (300 MHz, CDCl₃) δ = 8.49 (ddd, *J* = 8.0, 1.5, 0.6 Hz, 1H), 8.19 (ddd, *J* = 8.3, 1.2, 0.6 Hz, 1H), 7.68 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H), 7.51–7.39 (m, 4H), 7.31–7.27 (m, 2H), 3.28 (s, 3H), 1.62 (tt, *J* = 8.3, 5.6 Hz, 1H), 0.69–0.55 (m, 2H), 0.17–0.05 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ = 162.8 (C), 142.9 (C), 138.0 (C), 135.7 (C), 133.7 (CH), 129.9 (CH), 128.4 (CH), 128.4 (CH), 127.9 (CH), 126.2 (CH), 125.1 (C), 124.4 (CH), 115.0 (C), 34.2 (CH₃), 10.5 (CH), 8.7 (CH₂); IR (ATR): 3081, 2994, 2957, 2924, 1643, 1587, 1025, 759 cm^{−1}. MS (EI) *m/z* (%): 275 (M⁺, 32), 274 (100), 246 (15), 198 (27), 77 (30); HRMS (EI) calcd for C₁₉H₁₇NO (M⁺) 275.1310, found 275.1298. The structure of compound **8aa** was established by X-ray crystal structure analysis.¹³

4-CYCLOPROPYL-6-METHOXY-2-METHYL-3-PHENYLISOQUINOLIN-1(2*H*)-ONE (**8ha**) AND 3-CYCLOPROPYL-6-METHOXY-2-METHYL-4-PHENYLISOQUINOLIN-1(2*H*)-ONE (**9ha**). According to the general procedure, 4-methoxy-*N*-methylbenzamide (**5h**) (165 mg, 1.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), [RuCl₂(*p*-cymene)]₂ (31 mg, 50 μmol), and Cu(OAc)₂·H₂O (399 mg, 2.0 mmol) yielded **8ha** (173 mg, 56%) and **9ha** (9 mg, 3%) after column chromatography as colorless solids. **8ha**: m.p. = 135–137 °C; ¹H NMR (300 MHz, CDCl₃) δ = 8.39 (d, *J* = 8.9 Hz, 1H), 7.53 (d, *J* = 2.5 Hz, 1H), 7.48–7.37 (m, 3H), 7.29–7.23 (m, 2H), 7.04 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.91 (d, *J* = 1.5 Hz, 3H), 3.24 (d, *J* = 1.4 Hz, 3H), 1.57 (tt, *J* = 8.2, 5.6 Hz, 1H), 0.63–0.54 (m, 2H), 0.13–0.05 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ = 162.3 (C), 162.2 (C), 143.5 (C), 140.0 (C), 135.6 (C), 129.9 (CH), 129.8 (CH), 128.3 (CH), 119.0 (C), 115.1 (C), 114.4 (C), 109.1 (C), 106.9 (CH), 55.2 (CH₃), 33.9 (CH₃), 10.4 (CH), 8.6 (CH₂); IR (ATR): 2991, 2939, 2914, 1639, 1604, 1275, 1027, 779,

725, 687 cm^{-1} ; MS (EI) m/z (%): 305 (M^+ , 52), 304 (84), 274 (100), 228 (68), 185 (20), 118 (30), 84 (40), 77 (46); HRMS (EI) calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2$ (M^+) 305.1416; found: 305.1416.

9ha: m.p. = 145–147 $^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ = 8.39 (d, J = 8.9 Hz, 1H), 7.47–7.33 (m, 3H), 7.28 (d, J = 1.7 Hz, 1H), 7.25 (t, J = 1.5 Hz, 1H), 6.99 (dd, J = 8.9, 2.5 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 1.72 (tt, J = 8.3, 5.7 Hz, 1H), 0.75–0.66 (m, 2H), 0.34–0.25 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ = 162.6 (C), 162.3 (C), 140.8 (C), 138.9 (C), 137.3 (C), 131.4 (CH_2), 129.9 (CH), 128.3 (CH), 127.1 (CH), 119.4 (C), 118.7 (C), 115.0 (CH), 106.5 (CH), 55.2 (CH_3), 32.1 (CH_3), 14.0 (CH), 10.2 (CH_2); IR (ATR): 3057, 2974, 2939, 2914, 1643, 1586, 1225, 1025, 781, 705 cm^{-1} ; MS (EI) m/z (%): 305 (M^+ , 94), 290 (100), 277 (33), 152 (21), 82 (13), 41 (10); HRMS (EI) calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2$ (M^+) 305.1416; found: 305.1417.

Acknowledgements

Support by Astra-Zeneca and the EPSRC (UK) is gratefully acknowledged.

Notes and references

- (a) *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2nd edn, 2004; (b) *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 2nd edn, 2004.
- For selected recent reviews on C–H bond functionalization, see: (a) *Acc. Chem. Res.*, 2012, **45**, special issue 6 “C–H Functionalization”; (b) L. Ackermann, A. R. Kapdi, H. K. Potukuchi and S. I. Kozhushkov, in *Handbook of Green Chemistry*, ed. C.-J. Li, Wiley-VCH, Weinheim, 2012, pp. 259–305; (c) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345; (d) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215–1292; (e) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293–1314; (f) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902–4911; (g) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068–5083; (h) Y. Nakao, *Synthesis*, 2011, 3209–3219; (i) L. Ackermann and H. K. Potukuchi, *Org. Biomol. Chem.*, 2010, **8**, 4503–4513; (j) *Chem. Rev.*, 2010, **110**, special issue 2 “Selective Functionalization of C–H Bonds” (k) L. Ackermann, R. Vicente and A. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (l) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (m) F. Bellina and R. Rossi, *Tetrahedron*, 2009, **65**, 10269–10310; (n) A. A. Kulkarni and O. Daugulis, *Synthesis*, 2009, 4087–4109; (o) L. Joucla and L. Djakovitch, *Adv. Synth. Catal.*, 2009, **351**, 673–714; (p) *Modern Arylation Methods*, ed. L. Ackermann, Wiley-VCH, Weinheim, 2009; (q) L. Ackermann, *Top. Organomet. Chem.*, 2007, **24**, 35–60; (r) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (s) D. R. Stuart and K. Fagnou, *Aldrichimica Acta*, 2007, **40**, 35–41; (t) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173–1193; (u) L. Ackermann, *Synlett*, 2007, 507–526; (v) T. Satoh and M. Miura, *Chem. Lett.*, 2007, **36**, 200–205.
- For selected examples, lifespan-altering activity towards eukaryotic organisms: (a) D. S. Goldfarb, *US Pat.*, US 20090163545 A1, 2009, antituberculosis properties; (b) I. V. Ukrainets, L. V. Sidorenko, O. V. Gorokhova, V. B. Rybakov, V. V. Chernyshev and E. V. Kolesnik, *Visn. Farm.*, 2004, 7–12; modulation of PI3 kinase: (c) P. Ren, Y. Liu, T. E. Wilson, L. Li, K. Chan and C. Rommel, *PCT Int. Appl.*, WO 2011008302 A1, 2011; (d) P. Ren, Y. Liu, T. E. Wilson, L. Li, K. Chan and C. Rommel, *U.S. Pat. Appl.*, US 20090312319 A1, 2009; antifungal, antibacterial, and antidiabetic effects; (e) S. Cai, F. Wang and C. Xi, *J. Org. Chem.*, 2012, **77**, 2331–2336, and references cited therein; (f) V. Rukachaisirikul, A. Rodglin, Y. Sukpondma, S. Phongpaichit, J. Buatong and J. Sakayaroj, *J. Nat. Prod.*, 2012, **75**, 853–858; (g) W. K. Liu, Y. H. Ling, F. W. K. Cheung and C.-T. Che, *J. Nat. Prod.*, 2012, **75**, 586–590; (h) E.-J. Park, E. Kiselev, M. Conda-Sheridan, M. Cushman and J. M. Pezzuto, *J. Nat. Prod.*, 2012, **75**, 378–384; (i) R. J. R. Jaeger and P. Spiteller, *J. Nat. Prod.*, 2010, **73**, 1350–1354; (j) M. Kumarihamy, F. R. Fronczek, D. Ferreira, M. Jacob, S. I. Khan and N. P. D. Nanayakkara, *J. Nat. Prod.*, 2010, **73**, 1250–1253; (k) J. Kornsakulkarn, C. Thongpanchang, S. Lapanun and K. Srichomthong, *J. Nat. Prod.*, 2009, **72**, 1341–1343; (l) E. D. de Silva, A.-S. Geiermann, M. I. Mitova, P. Kuegler, J. W. Blunt, A. L. J. Cole and M. H. G. Munro, *J. Nat. Prod.*, 2009, **72**, 477–479.
- For selected recent reports on ruthenium-catalyzed C–H/O–H and C–H/N–H bond functionalization, see: (a) K. Parthasarathy, N. Senthilkumar, J. Jayakumar and C.-H. Cheng, *Org. Lett.*, 2012, **14**, 3478–3481; (b) V. S. Thirunavukkarasu, M. Donati and L. Ackermann, *Org. Lett.*, 2012, **14**, 3416–3419; (c) R. K. Chinnagolla, S. Pimparkar and M. Jeganmohan, *Org. Lett.*, 2012, **14**, 3032–3035; (d) L. Ackermann and A. V. Lygin, *Org. Lett.*, 2012, **14**, 764–767; (e) R. K. Chinnagolla and M. Jeganmohan, *Chem. Commun.*, 2012, 2030–2032; (f) L. Ackermann, J. Pospech, K. Graczyk and K. Rauch, *Org. Lett.*, 2012, **14**, 930–933; (g) L. Ackermann, L. Wang and A. V. Lygin, *Chem. Sci.*, 2012, **3**, 177–180; (h) B. Li, H. Feng, S. Xu and B. Wang, *Chem.-Eur. J.*, 2011, **17**, 12573–12577; (i) L. Ackermann and S. Fenner, *Org. Lett.*, 2011, **13**, 6548–6551; (j) L. Ackermann, A. V. Lygin and N. Hofmann, *Org. Lett.*, 2011, **13**, 3278–3281; (k) L. Ackermann, A. V. Lygin and N. Hofmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 6379–6382. For recent reviews on ruthenium-catalyzed C–H bond functionalization, see: (l) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, DOI: 10.1021/cr300153j; (m) L. Ackermann, *Pure Appl. Chem.*, 2010, **82**, 1403–1413; (n) L. Ackermann and R. Vicente, *Top. Curr. Chem.*, 2010, **292**, 211–229.

- 5 For reviews on intermolecular C–H/O–H and C–H/N–H cyclizations with alkynes catalyzed by metals other than ruthenium see: (a) C. Zhu, R. Wang and J. R. Falck, *Chem.-Asian J.*, 2012, **7**, 1502–1514; (b) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740–4761; (c) T. Satoh and M. Miura, *Synthesis*, 2010, 3395–3409; (d) T. Satoh, K. Ueura and M. Miura, *Pure Appl. Chem.*, 2008, **80**, 1127–1134. Representative communications: (e) B.-J. Li, H.-Y. Wang, Q.-L. Zhu and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2012, **51**, 3948–3952; (f) H. Zhong, D. Yang, S. Wang and J. Huang, *Chem. Commun.*, 2012, 3236–3238; (g) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449–6457; (h) T. Satoh and M. Miura, *Chem.-Eur. J.*, 2010, **16**, 11212–11222; (i) K. Ueura, T. Satoh and M. Miura, *J. Org. Chem.*, 2007, **72**, 5362–5367; (j) K. Ueura, T. Satoh and M. Miura, *Org. Lett.*, 2007, **9**, 1407–1409.
- 6 Reviews: (a) C. J. Thibodeaux, W.-C. Chang and H.-W. Liu, *Chem. Rev.*, 2012, **112**, 1681–1709; (b) F. Brackmann and A. de Meijere, *Chem. Rev.*, 2007, **107**, 4493–4583; (c) L. A. Wessjohann, W. Brandt and T. Thiemann, *Chem. Rev.*, 2003, **103**, 1625–1648; (d) F. Gnad and O. Reiser, *Chem. Rev.*, 2003, **103**, 1603–1624; (e) J. Salaün, *Top. Curr. Chem.*, 2000, **207**, 1–67; (f) J. Salaün and M. S. Baird, *Curr. Med. Chem.*, 1995, **2**, 511–542.
- 7 (a) P. von R. Schleyer, J. E. Williams Jr. and K. P. Blanchard, *J. Am. Chem. Soc.*, 1970, **92**, 2377–2386; (b) R. D. Bach and O. Dmitrienko, *J. Am. Chem. Soc.*, 2004, **126**, 4444–4452, and references cited therein.
- 8 Selected reviews on metal-promoted reactions of substituted cyclopropanes: (a) C. Aïssa, *Synthesis*, 2011, 3389–3407; (b) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, 2007, **107**, 3117–3179; (c) I. Nakamura and Y. Yamamoto, *Adv. Synth. Catal.*, 2002, **344**, 111–129, and references cited therein. Selected rare metal-catalyzed reactions, not resulting in an opening of at least one cyclopropane ring: (d) L. Ackermann, S. I. Kozhushkov and D. S. Yufit, *Chem.-Eur. J.*, 2012, **18**, 12068–12077; (e) T.-L. Liu, Z.-L. He, H.-Y. Tao, Y.-P. Cai and C.-J. Wang, *Chem. Commun.*, 2011, 2616–2618; (f) Y. Fall, H. Doucet and M. Santelli, *Tetrahedron*, 2010, **66**, 2181–2188; (g) M. Shirakura and M. Sugimoto, *J. Am. Chem. Soc.*, 2009, **131**, 5060–5061; (h) S. I. Kozhushkov, D. S. Yufit and L. Ackermann, *Org. Lett.*, 2008, **10**, 3409–3412 and references cited therein.
- 9 Selected examples: (a) S. I. Kozhushkov, T. Späth, M. Kosa, Y. Apeloig, D. S. Yufit and A. de Meijere, *Eur. J. Org. Chem.*, 2003, 4234–4242, and references cited therein; (b) G. Boche and H. M. Walborsky, *Cyclopropane Derived Reactive Intermediates*, ed. S. Patai and Z. Rappoport, Wiley, Chichester, 1990, pp. 117–173; (c) A. de Meijere, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 809–826.
- 10 Steric substituent constants of the *n*-propyl and cyclopropyl moieties are equal to 0.89 and 1.33, respectively: H. D. Beckhaus, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 593–594.
- 11 The structures of selected regioisomers have been established by X-ray crystal structure analysis: J. Langer, M. Gärtner, H. Görls and D. Walther, *Synthesis*, 2006, 2697–2706; or by their properties with those of the probes, independently prepared by alternative procedures.¹²
- 12 (a) R. Rossi, A. Carpita, F. Bellina, P. Stabile and L. Mannina, *Tetrahedron*, 2003, **59**, 2067–2081; (b) J. Delaunay and J. Simonet, *Tetrahedron Lett.*, 1988, **29**, 543–544; (c) J. N. Chatterjea, S. K. Mukherjee, C. Bhakta, H. C. Jha and F. Zilliken, *Chem. Ber.*, 1980, **113**, 3927–3931; (d) H. E. Zimmerman and R. D. Simkin, *Tetrahedron Lett.*, 1964, 1847–1851.
- 13 CCDC 901337 (**6aa**), 901338 (**6ae**), 901339 (**7aa**), 901340 (**8aa**) and 901341 (**8ah**) contain the supplementary crystallographic data for this paper.
- 14 Only in the reaction of substituted alkyne **4b** with **2g** we have observed traces of a by-product with the same molecular mass as the one of product **7bg**.†
- 15 Several representative cyclopropyl-substituted isocoumarins and isoquinolones were prepared by multistep syntheses through cyclizations of functionalized *ortho*-alkynylbenzoates under gold, palladium and rhodium catalysis: (a) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Ackermann, J. De Buck Becker, M. Rudolph, C. Scholz and F. Rominger, *Adv. Synth. Catal.*, 2012, **354**, 133–147; (b) A. Fürstner and P. W. Davies, *J. Am. Chem. Soc.*, 2005, **127**, 15024–15025; (c) P. Zhao, D. Chen, G. Song, K. Han and X. Li, *J. Org. Chem.*, 2012, **77**, 1579–1584.